



Bronchiectasis Patient-Centered Research Priorities and Roadmap

December 29, 2016

This research roadmap, developed in collaboration with patients, will provide essential direction for future bronchiectasis research.

This project was funded through a Patient-Centered Outcomes Research Institute (PCORI) Eugene Washington PCORI Engagement Award (#2651)

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EXECUTIVE SUMMARY

Dear Bronchiectasis Community,

In the past few years we have seen an encouraging trend in the conduct of medical research. “Patient-centered research” has emerged, placing a high priority on incorporating the voice and view of the patient into the development of medical studies. With the help of the Patient Centered Outcomes Research Institute (PCORI) and our partners, this movement has finally arrived in the area of bronchiectasis. Together with scientists and physicians, patients assist to set research priorities, help design studies that answer questions relevant to them, and collaborate in interpreting the outcomes of such studies. Patients provide perspective on living with their diagnosis of bronchiectasis and what is needed to improve their treatment and health-related quality of life. PCORI calls this new way of conducting research “research done differently”, and we hope the change is lasting.

This Bronchiectasis Research Roadmap is a thoughtful, timely document that incorporates patient and clinical stakeholder input. Bronchiectasis is a rare, but increasingly common chronic lung disease that has few treatment options that have been rigorously examined. Patients endure a chronic cough and infectious exacerbations that are often difficult to manage. Evidence of risks and benefits of treatments are needed. The priority areas with specific objectives and next steps included in this roadmap provide a description of needs and a path to move the field forward in a patient-focused manner.

We thank the many patients and stakeholders who came together to participate in the discussion and complete the needs assessment survey, particularly our 7-member Patient Advisory Panel and patients who are part of the bronchandntm360social.org network supported by the COPD Foundation and NTM Info & Research.



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INTRODUCTION

BACKGROUND

Bronchiectasis is a rare, chronic, inflammatory lung disease that has a marked impact on quality of life. An estimated 100,000 adults over 65 are living with bronchiectasis and nearly 200,000 overall in the United States (U.S.).¹² While this condition is associated with cystic fibrosis (CF), most patients do not have CF and have what is termed “non-CF” bronchiectasis (referred to as bronchiectasis throughout this document). Bronchiectasis predominantly affects females and incidence increases with age, with most patients over the age of 60 years old.

Bronchiectasis is an inflammatory condition characterized by dilated, inflamed, and damaged airways. It is distinct from chronic obstructive pulmonary disease (COPD), although patients with bronchiectasis can develop obstructive lung disease. Patients with bronchiectasis suffer chronic productive cough, debilitating weakness and fatigue, dyspnea, hemoptysis, and are at high risk for recurrent pneumonia and death due to lung infections. Acute infectious bacterial exacerbations are a hallmark and regular complication characterized by increased respiratory symptoms, decreased health-related quality of life, loss of lung function, and the need for antibiotics. Exacerbations often result in hospitalization and are associated with increased health care costs, and most importantly, lead to progression of airway damage and dilatation. In most, but not all cases, exacerbations are associated with infections. Important pathogens in this setting include bacterial organisms such as *Pseudomonas aeruginosa* and *Haemophilus influenzae*.³ Chronic infections with nontuberculous mycobacteria (NTM) such as *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* can cause or worsen underlying bronchiectasis. These infections can markedly affect health-related quality of life, and chronic disability can greatly diminish individual participation in social, occupational, and recreational activities.

In 2013 we collaborated with NTM Info & Research (NTMir, a national NTM patient advocacy organization) to conduct an electronic survey of bronchiectasis patients from among the 2000 total members. A total of 511 patients with bronchiectasis responded to questions about research priorities and impacts of bronchiectasis disease.⁴ The quotes below taken directly from our pilot survey highlight patient concerns about their bronchiectasis diagnosis:

¹ A. E. O'Donnell, "Bronchiectasis," *Chest* 134, no. 4 (2008).

² A. E. Seitz et al., "Trends in Bronchiectasis among Medicare Beneficiaries in the United States, 2000 to 2007," *ibid.* 142, no. 2 (2012).

³ P. C. Goeminne et al., "Risk Factors for Morbidity and Death in Non-Cystic Fibrosis Bronchiectasis: A Retrospective Cross-Sectional Analysis of Ct Diagnosed Bronchiectatic Patients," *Respir Res* 13 (2012).

⁴ E. Henkle, "Patterns of Pharmacotherapy for Non-Cf Bronchiectasis" (paper presented at the American Thoracic Society, Denver, CO, 2015).

- (1) "My pulmonologist doesn't seem to think it's a big deal to have this and just says to keep on the Advair."
- (2) "Dismay of lack of understanding by medical practice, lack of understanding about degree of seriousness."
- (3) "Greatest bronchiectasis concern is how to stop its progression"
- (4) "Lack of training and info to improve symptoms and quality of life... what is best?"
- (5) "My biggest concern is that it increases my risk of repeated [NTM] infection. And there is nothing I can do to reverse the damage."

The quotes above reflect the uncertainty in treatment and prognosis for bronchiectasis patients. The goals of treatment are to improve symptoms, reduce airway inflammation, limit further bronchiectasis progression, and prevent chronic lung infection and acute symptomatic infectious exacerbations. There are no published U.S. guidelines for bronchiectasis treatment, but in 2010 the British Thoracic Society (BTS) produced guidelines summarizing current therapies.⁵ This guideline revealed a lack of safety and effectiveness data to guide treatment and highlighted the need for research in many aspects of this disease. It did not, however, discuss utilizing a patient-centered approach, and to date, there has been little attention to patient input. One new area, in which patient input is systematically sought, is the development of patient-reported outcomes, such as measures of health-related quality of life. In a series of qualitative and quantitative studies, patient input was instrumental in the development of the Quality of Life-Bronchiectasis instrument (QOL-B).^{6,7}

A number of new therapies are in development, including inhaled formulations of ciprofloxacin and other inhaled or oral antibiotics. These and other studies need input regarding which interventions are most appealing or concerning to patients, and which outcome measures are most important to patients. Given that the goals of therapy involve maintaining quality of life and minimizing disease progression, and given the routine use of a number of untested or unproven therapies (e.g. steroids, bronchodilators, hypertonic saline, others), we believe that both prioritizing research questions and studying outcomes of interest to patients will provide the most efficient progress in caring for patients with this disease. This research roadmap, developed in collaboration with patients, will provide essential direction for future bronchiectasis research.

⁵M. C. Pasteur et al., "British Thoracic Society Guideline for Non-Cf Bronchiectasis," *Thorax* 65 Suppl 1 (2010).

⁶A. L. Quittner et al., "A Preliminary Quality of Life Questionnaire-Bronchiectasis: A Patient-Reported Outcome Measure for Bronchiectasis," *Chest* 146, no. 2 (2014).

⁷A. L. Quittner et al., "Quality of Life Questionnaire-Bronchiectasis: Final Psychometric Analyses and Determination of Minimal Important Difference Scores," *Thorax* 70, no. 1 (2015).

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TIMELINE

April 2016	Develop needs assessment survey with Patient Advisory Panel input.
May to November 2016	Anonymous patient needs assessment survey available to public.
August 2016	Webinar to discuss preliminary survey results with Stakeholders.
September 2016	Draft roadmap.
October-November 2016	Gather feedback from Stakeholders and patients on bronchandntm360social.
November 2016	Discuss objectives, next steps with Stakeholders.
December 2016	Final Stakeholder consensus survey of objectives and next steps.
December 2016	Finalize roadmap document.

NEEDS ASSESSMENT SURVEY

The Needs Assessment survey was conducted electronically and anonymously using an online SurveyMonkey™ survey. Patients were invited to complete the survey using a number of different mechanisms: Bronchiectasis and NTM Research Registry letters, on bronchandntm360social.org posts, emails to COPD Foundation and NTMir communities, and publications in the COPD Digest. Overall the survey patient population (N=459 with a self-reported diagnosis of bronchiectasis) reflected the general population with bronchiectasis. Most (70%) were between 50 and 79 and 87% were female; 17% had no listed underlying condition, 25% had a COPD diagnosis, 20% had a genetic condition (other than CF) predisposing them to bronchiectasis, and a total of 56% had any current or past history of NTM. See Figures 1 to 4 below for responses by age group, sex, region, and underlying condition.

FIGURE 1: RESPONDENT AGE GROUPS

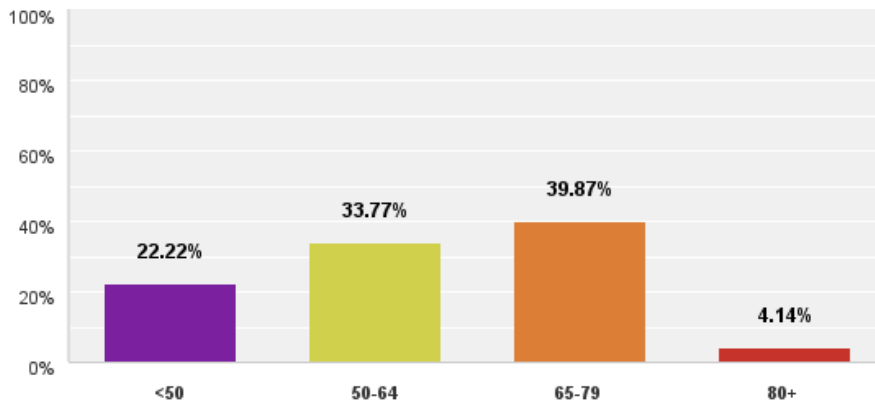


FIGURE 2: RESPONDENT SEX

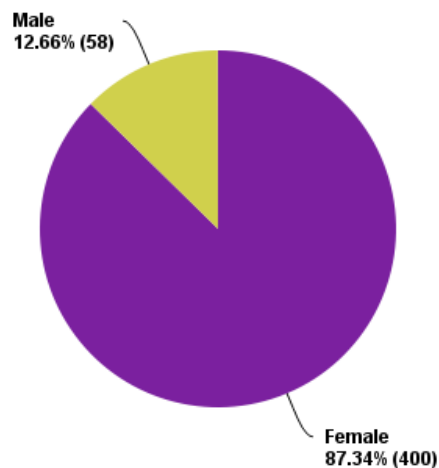


FIGURE 3: RESPONDENT GEOGRAPHIC LOCATION

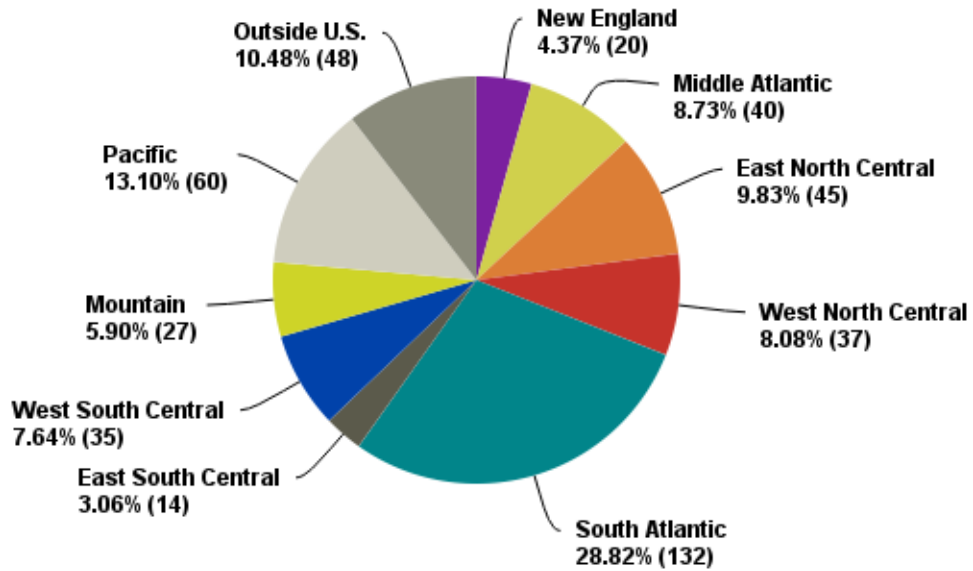
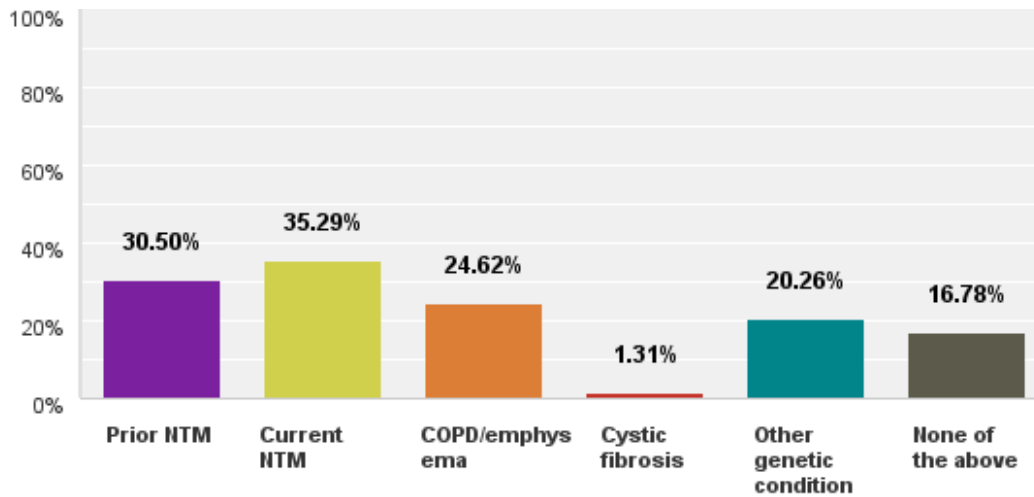


FIGURE 4: RESPONDENT UNDERLYING CONDITIONS



THE RESEARCH ROADMAP

During the past year, clinical and patient stakeholders have identified the following six broad priorities for bronchiectasis research:

1. Improve treatment of bronchiectasis and prevent exacerbations
2. Improve treatment of exacerbations and associated infections
3. Improve health-related quality of life
4. Identify predictors of poor prognosis
5. Understand impact of underlying conditions
6. Conduct patient-centered clinical trials

We discuss each of these in more detail as well as describing ways to strengthen or expand current research efforts. Where applicable, specific research objectives are provided. The objectives are not ranked.

PRIORITY 1: IMPROVE TREATMENT OF BRONCHIECTASIS AND PREVENT EXACERBATIONS

Bronchiectasis has been characterized by a cycle of airway infection, inflammation, and progressive airway injury leading to irreversible bronchial tube dilation and propagation of additional airway infection, inflammation, and injury.⁸ The goals of bronchiectasis therapy are to improve symptoms, maintain quality of life, reduce exacerbations, and prevent disease progression. Over 75% of survey responders selected treatment of bronchiectasis as one of their top 3 research priorities. When limited to a single therapeutic priority, 52% selected bronchiectasis treatment and 14% selected complementary or alternative therapy. Prevention of exacerbations was the second most commonly selected research priority, selected as one of the top 3 priorities by 54% of survey respondents.

We know that a number of untested or unproven therapies (e.g. steroids, bronchodilators, hypertonic saline, others) are routinely used to treat patients with bronchiectasis (Table 1). During the prior year, 62% of survey responders reported taking inhaled corticosteroids and 24% reported taking oral steroids for at least 30 days in a row. Clinicians recommend airway clearance devices, presenting patients with the various options and working with patients to determine which works best for them without evidence of comparative effectiveness. Airway clearance is a daily, time-intensive therapy for patients who typically spend 30 to 60 minutes per day to clear their lungs. Despite this, 55% of survey respondents reported using positive expiratory pressure (PEP) therapy, 27% reported using the vest/chest oscillation, and 8% reported using a lung flute.

TABLE 1. PHARMACOTHERAPIES AND AIRWAY CLEARANCE DEVICES USED IN BRONCHIECTASIS

Anti-inflammatory		Bronchodilators		Mucous/ airway clearance
Inhaled steroids	beclomethasone	Short acting	albuterol	inhaled hypertonic saline vibratory positive expiratory pressure chest physiotherapy/ percussive therapy
	budesonide		levabuterol	
	flunisolide		pirbuterol	
	fluticasone	Long acting	formoterol	
mometasone	tiotropium			
	triamcinolone		salmeterol	
Combined steroid/ bronchodilator	ipatropium/albuterol			
	budesonide/formoterol			
	fluticasone/salmeterol			
Oral steroids	prednisone			
Macrolide antibiotics	azithromycin*erythromycin*			

*tested in randomized clinical trials for bronchiectasis

⁸P. J. McShane, E. T. Naureckas, and M. E. Streck, "Bronchiectasis in a Diverse Us Population: Effects of Ethnicity on Etiology and Sputum Culture," *Chest* 142, no. 1 (2012).

Acute exacerbations are typically but not exclusively associated with respiratory infections. To prevent infectious exacerbations, antibiotics may be given to eradicate bacteria (e.g. *Pseudomonas*) or as suppressive therapy to reduce bacterial burden. Suppressing antibiotics, including inhaled tobramycin, gentamicin, and colistin are used “off-label” for patients with bronchiectasis. However, evidence of a benefit of inhaled antibiotics in patients with bronchiectasis is lacking. Two Phase 3 randomized placebo-controlled trials of inhaled aztreonam did not provide clinical benefits in bronchiectasis patients.⁹ Results from two Phase 3 randomized clinical trials of two formulations of inhaled ciprofloxacin are expected in the near future. Other important areas that need further research include the role of rotating antibiotics and optimal duration and dosing schedule for suppressive antibiotics.

OBJECTIVES

- 1.1 Rigorously evaluate the efficacy and safety of long term use of inhaled corticosteroids in bronchiectasis.
- 1.2 Compare the effectiveness of physical airway clearance techniques, accounting for patient preference and adherence.
 - Vibratory positive expiratory pressure
 - Percussion therapy/ chest physiotherapy
- 1.3 Evaluate the efficacy of mucolytics and hypertonic saline in bronchiectasis.
- 1.4 Evaluate the efficacy of bronchodilators in bronchiectasis.
- 1.5 Evaluate the efficacy and safety of inhaled antibiotics to prevent exacerbations.
- 1.6 Evaluate naturopathic and alternative therapies to reduce inflammation.

⁹A. F. Barker et al., "Aztreonam for Inhalation Solution in Patients with Non-Cystic Fibrosis Bronchiectasis (Air-Bx1 and Air-Bx2): Two Randomised Double-Blind, Placebo-Controlled Phase 3 Trials," *Lancet Respir Med* 2, no. 9 (2014).

Treatment of infections (50% of survey respondents) and exacerbations (44%) were the 3rd and 4th ranked research priorities. Among bronchiectasis treatment priorities 33% of survey respondents selected treatment of exacerbations or associated infections as the top priority. Acute infectious exacerbations may occur 3-6 times per year. However, the nature of acute exacerbations has not been rigorously studied nor has a standardized management approach been established. Specifically, the very definition of an acute exacerbation of bronchiectasis has varied across clinical trials and amongst clinicians. Consensus agreement on the definition of an exacerbation will be critical to more meaningful clinical trials and an understanding of the natural course of the disease process.

It is understood that the airways are home to diverse communities of microbiologic organisms, and that this “microbiome” of the normal airway changes in bronchiectasis patients.^{10,11} What remains unknown is how best to approach the microbiology in the context of antibiotic treatment selection during an acute exacerbation. Historically, respiratory samples have been cultured at the time of the acute exacerbation and antibiotic treatment decisions were made based on these culture results. However, this may not be the best approach and questions about the importance of historical culture and susceptibility results need to be examined.

The only published treatment guidelines regarding the length of antibiotic treatment, which varies by targeted organism, are based primarily on expert opinion.¹² These guidelines from the United Kingdom may not be equally applicable to all types of bronchiectasis patients or to the approach to exacerbations in other geographic regions. Moreover, it is unclear as to whether clearing a specific bacterial organism from respiratory culture means the organism has been eradicated from the airways or even whether it is a reasonable goal of treatment.

The choice of specific antibiotic to treat an acute infectious exacerbation of based on *in vitro* susceptibilities of organism isolated is under question as well. In the case of CF- associated bronchiectasis, data is available that *in vivo* clinical responses do not correlate with *in vitro* susceptibility results for treatment of acute exacerbations.¹³ This differs greatly from the accepted approach to treating *M. tuberculosis* (TB) or systemic bacterial infections in which *in*

¹⁰M. M. Tunney et al., "Lung Microbiota and Bacterial Abundance in Patients with Bronchiectasis When Clinically Stable and During Exacerbation," *Am J Respir Crit Care Med* 187, no. 10 (2013).

¹¹R. P. Dickson, F. J. Martinez, and G. B. Huffnagle, "The Role of the Microbiome in Exacerbations of Chronic Lung Diseases," *Lancet* 384, no. 9944 (2014).

¹²Pasteur et al., "British Thoracic Society Guideline for Non-CF Bronchiectasis," *Thorax* 65 Suppl 1 (2010).

¹³A. L. Smith et al., "Susceptibility Testing of Pseudomonas Aeruginosa Isolates and Clinical Response to Parenteral Antibiotic Administration: Lack of Association in Cystic Fibrosis," *Chest* 123, no. 5 (2003).

vitro drug susceptibility testing guides antibiotic selection.¹⁴ In part, the differences may reflect the complexities of the diverse population of organisms in the airways of bronchiectasis patients in contrast to singular infectious organisms as is the case with TB or bacteremia.

Last, the meaningfulness of the specific bacterial pathogens isolated in respiratory secretions is an area in need of additional investigation. It has long been known that the presence of *Pseudomonas* in respiratory secretions is associated with increased symptoms, accelerated loss of lung function, and more frequent exacerbations.¹⁵ Whether other organisms isolated at the time of exacerbation have similar impact on prognosis is unclear. In addition, the treatment of chronic co-infections such as NTM or fungi (e.g. *Aspergillus*) that are common in bronchiectasis patients and cause decline is important. NTM treatment guidelines have been published and are in the process of being updated.¹⁶ However, the role of these chronic co-infections on the approach to the treatment of acute exacerbations due to other organisms is not clear.

OBJECTIVES

- 2.1 Establish a standardized definition of exacerbation of bronchiectasis.
- 2.2 Explore the impact of specific elements of symptoms and signs of exacerbations on the sensitivity and specificity of exacerbation definition.
- 2.2 Evaluate the role of culture of respiratory secretions at baseline and during exacerbations on the impact of response to antibiotics and clinical outcomes.
- 2.3 Evaluate the utility of *in vitro/in vivo* antibiotic susceptibility testing for guiding antibiotic treatment regimens.
- 2.4 Evaluate the optimal duration of antibiotics for the treatment of acute infectious exacerbations of bronchiectasis.
- 2.5 Establish updated and more broadly applicable guidelines to the approach of acute exacerbations of bronchiectasis.
- 2.6 Update treatment guidelines for chronic co-infections with pathogens including NTM.

¹⁴P. Nahid et al., "Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis," *Clin Infect Dis* 63, no. 7 (2016).

¹⁵C. B. Wilson et al., "Effect of Sputum Bacteriology on the Quality of Life of Patients with Bronchiectasis," *Eur Respir J* 10, no. 8 (1997).

¹⁶D. E. Griffith et al., "An Official Ats/Idsa Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases," *Am J Respir Crit Care Med* 175, no. 4 (2007).

Bronchiectasis has a major impact on patients' health-related quality of life. It is a chronic, progressive disease that must be managed, since it is only rarely cured with surgery. The symptom burden associated with bronchiectasis is significant and can interfere with daily activities and physical, social and emotional functioning. Chronic respiratory symptoms, such as cough and sputum production, can be hard to manage in social situations, and can cause fatigue and difficulties with sleep. Most individuals have to do treatments, such as airway clearance and inhaled medications, which take between 60 and 120 minutes a day. The top two priorities for survey respondents in relation to health-related quality of life were: 1) improving the impact of the disease on daily life (54%) and 2) reducing treatment burden (28%). Although not ranked as highly, other priorities included how bronchiectasis affects social interactions (12%) and risks for development of depression or anxiety (6%).

There are several ways to reduce treatment burden. One is to develop devices that shorten treatment time. A good example of that is the new tobramycin inhalation powder device, which decreases treatment time from 40 minutes a day to about five minutes. Another way to reduce burden is to simplify administration of the medication. The tobramycin inhalation powder device consists of disposable capsules with no need to clean or sanitize equipment. This device is also portable so that people can travel more easily.

Based on results of the survey, the health-related quality of life objectives are to reduce treatment burden and identify effective traditional and complementary therapies. The QOL-B has a Treatment Burden scale which can be used to measure whether a new mode of administration reduces burden. Another purpose of the QOL-B is to serve as a primary or secondary outcome measure in clinical trials of new medications or treatments. The U.S. Food and Drug Administration (FDA) and European Medicines Agency now accept patient-reported outcomes as evidence of efficacy, particularly scales that measure key symptoms (e.g., improvement in respiratory symptoms).

OBJECTIVES

- 3.1 Consider time and ease of administration in the development of new drugs.
- 3.2 Measure the efficacy of new pharmaceutical and complementary treatments including acupuncture, exercise, diet, massage, relaxation training, and yoga/mindfulness.

PRIORITY 4: IDENTIFY PREDICTORS OF POOR PROGNOSIS

Bronchiectasis is diagnosed by findings on a high resolution CT scan. Although diagnosis may be delayed, the impact of this delay on prognosis is not known. Once diagnosed, survey respondents were most interested in measuring disease severity and improving provider education about bronchiectasis. Clinician education about bronchiectasis applies across all priorities, and will be addressed in the “Moving Forward” section. With regards to prognosis, 45% of survey respondents selected biomarkers (“items in your blood that indicate more rapidly progressing disease or higher risk for complications”) as the top priority and 25% prioritized severity measures. Biomarkers and severity measures are combined as predictors of poor prognosis in this section.

As defined by the Biomarker Definitions Working Group¹⁷, “a biological marker or biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.” A biomarker may be measured using a radiologic exam, quantification of a substance in the blood, urine, sweat, saliva, or cerebral spinal fluid, or identification of a genetic variation.¹⁷ A biomarker that predicts poor prognosis can be used in the clinical setting to identify patients who may benefit from therapy or those who will not, or those who are at low risk from progression and do not need therapy at that time. In addition to predictors of poor prognosis, biomarkers may be used to measure drug toxicity or as surrogate endpoint in clinical trials.

Biomarkers must undergo rigorous examination prior to use in clinical and clinical trial settings. A good biomarker is sensitive, specific, and easily reproduced (See Table for definitions). Biomarkers must correlate with clinical measures of disease progression or severity. Last, the technology used to measure the biomarker must be relatively easy to implement in routine practice.

TABLE: BIOMARKER CHARACTERISTIC DEFINITIONS

Characteristic	Definition
Sensitive	Proportion who test “positive” given that they have disease/abnormal pathology
Specific	Proportion who test “negative” given no disease/normal pathology
Reproducible	Stable measurements within an individual across short periods of time

¹⁷Group Biomarkers Definitions Working, “Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework,” *Clin Pharmacol Ther* 69, no. 3 (2001).

Given the inflammatory nature of this disease, it is possible that inflammatory markers alone or in combination with subjective or objective clinical findings could be used as a measure of disease activity and serve as prognostic markers for disease progression. It is also possible that such markers would correlate with health-related quality of life measures. Currently there are no widely accepted biomarkers for disease severity or progression in bronchiectasis. However, recent studies have documented that sputum neutrophil elastase (NE) correlated with both disease severity and disease progression in patients with^{18,19} and without²⁰ CF. Because higher NE levels were associated with lung function decline and exacerbations, they may be useful as surrogate markers in clinical trials.

Several tools have been developed in Europe to measure disease severity: the Bronchiectasis Severity Index (BSI) and FACED score.^{21,22} The two scores, which group patients into mild, moderate, and severe categories were recently compared in a multicenter pooled analysis.²³ The BSI was consistently a good predictor of death, objective clinical outcomes (i.e. hospital admissions, exacerbations, lung function decline) and health-related quality of life measured by the QOL-B. The BSI, which takes into account more factors than the FACED score, incorporates age, predicted FEV1%, presence of chronic *Pseudomonas aeruginosa* isolation, radiologic characterization of bronchiectasis (number of lobes and type), degree of dyspnea, body mass index, exacerbation frequency, prior hospitalization for exacerbations, and chronic isolation of other bacteria. Further evaluation of the BSI tool is needed in a U.S. population, which is more diverse racially and with regards to underlying and associated conditions including nontuberculous mycobacterial (NTM) disease. Asian patients are at higher risk of bronchiectasis compared to White or African-American patients.²⁴

¹⁸ N. Mayer-Hamblett et al., "Association between Pulmonary Function and Sputum Biomarkers in Cystic Fibrosis," *Am J Respir Crit Care Med* 175, no. 8 (2007).

¹⁹ S. D. Sagel et al., "Sputum Biomarkers of Inflammation and Lung Function Decline in Children with Cystic Fibrosis," *ibid.* 186, no. 9 (2012).

²⁰ J. D. Chalmers et al., "Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis," *ibid.* (2016).

²¹ J. D. Chalmers et al., "The Bronchiectasis Severity Index. An International Derivation and Validation Study," *ibid.* 189, no. 5 (2014).

²² M. A. Martinez-Garcia et al., "Multidimensional Approach to Non-Cystic Fibrosis Bronchiectasis: The Faced Score," *Eur Respir J* 43, no. 5 (2014).

²³ M. J. McDonnell et al., "Multidimensional Severity Assessment in Bronchiectasis: An Analysis of Seven European Cohorts," *Thorax* (2016).

²⁴ Seitz et al., "Trends in Bronchiectasis among Medicare Beneficiaries in the United States, 200 to 2007." *Chest* 142 no. 2 (2012).

OBJECTIVES

- 4.1 Identify biomarker candidates.
- 4.2 Develop and evaluate biomarkers that can be used as predictors of poor prognosis.
- 4.3 Validate the BSI in the U.S. in a more diverse bronchiectasis population including Asian patients and those with NTM disease.
- 4.4 Validate the BSI as a predictor of exacerbations.
- 4.5 Evaluate the utility of BSI as a clinical tool to guide therapeutic choice.
- 4.6 Develop a disease activity score that takes into account subjective patient-reported outcomes.

We already distinguish patients with bronchiectasis associated with CF with those who do not. In fact, bronchiectasis is associated with a number of underlying conditions that cause the development of bronchiectasis, though in many cases it is considered idiopathic with no detected underlying cause. Just over 20% of survey respondents selected a better understanding of the impact of underlying diagnoses as the top priority for the general category of prognosis. Common conditions that impact bronchiectasis diagnosis and treatment include COPD and asthma. The following are some of the most important rare causes of bronchiectasis:

- CF transmembrane conductance regulator (CFTR) mutations
- Allergic bronchopulmonary aspergillosis (ABPA)
- Pulmonary ciliary dyskinesia
- Immune deficiency (e.g. common variable immune deficiency)
- Autoimmune disorders (e.g. Sjogren's syndrome, rheumatoid arthritis)
- Marfan's disease

Diagnosis and treatment of these and other underlying conditions is part of standard of care for patients with bronchiectasis. What is unclear is whether there are differences in treatment and prognosis, and how to prevent bronchiectasis development and progression.

OBJECTIVES

- 5.1 Describe the natural history of bronchiectasis in patients with different underlying and concomitant diagnoses.
- 5.2 Conduct subgroup analyses where possible to identify differences in treatment response or risks.

Modern research is increasingly being conducted with patient partners. The FDA “Patient-Focused Drug Development” initiative is gathering input from patients and clinical experts on 20 diseases. Funding agencies including PCORI increasingly require patients to be involved in study development and clinical trial recruitment as stakeholders. The purpose is to conduct meaningful clinical research in order to answer questions most relevant to patients.

The QOL-Bronchiectasis (QOL-B) survey is a validated, modern tool to measure health-related quality of life in patients with bronchiectasis. The CFQ-R, a similar tool which measures health-related quality of life in patients with CF, is a standard endpoint in clinical trials for CF. In the two Phase 3 randomized trials that used the QOL-B as a primary outcome, bronchiectasis patients scored the lowest on Respiratory Symptoms, Physical Functioning, Vitality, Health Perceptions, and Social Functioning.²⁵ Relatively higher scores were reported on Role Functioning, Emotional Functioning, and Treatment Burden. The Physical Functioning score was highly associated with lung function (FEV₁) at baseline. Slower 6-minute walk tests were associated with lower scores for Physical Functioning, Vitality, Role Functioning, and Health Perceptions in both studies, and Respiratory Symptoms and Emotional Functioning in one. Given the impact of bronchiectasis on health-related quality of life, we support the expanded use of QOL-B as a key patient-reported outcome for clinical trials. For patients with both bronchiectasis and NTM a complementary NTM symptom module has been developed and final validation is expected in 2017.²⁶

OBJECTIVES

- 6.1 Involve patients in the design of clinical trials for bronchiectasis.
- 6.2 Include the QOL-B as a primary or secondary outcome measure within all bronchiectasis clinical trials.
- 6.3 Include the NTM module for those with bronchiectasis and NTM.
- 6.4 Evaluate the correlation between health-related quality of life measures and treatment response.

²⁵Quittner et al. "Quality of Life Questionnaire-Bronchiectasis: Final Psychometric Analyses and Determination of Minimal Important Difference Scores." *Thorax* 70, no. 1 (2015).

²⁶A. L. Quittner, A. Madan, and E. Saez-Flores, "Development of a Quality of Life Measure for Nontuberculous Mycobacteria (Ntm) [Abstract]," in *ERS International Congress (Amsterdam2015)*.

To date, bronchiectasis has been considered a rare disease, though the prevalence is difficult to estimate. Chronic NTM infection is commonly associated with the diagnosis and is a feared outcome for patients with bronchiectasis. There is a growing interest internationally to better understand bronchiectasis and develop registries. In the U.S., the Bronchiectasis and NTM Research Registry (BRR) has enrolled over 2,000 bronchiectasis and NTM patients and collected up to 9 years of data on some patients since 2007.²⁷ The BRR was used as a model for the creation of the European Bronchiectasis Registry (www.bronchiectasis.eu/registry), which seeks to enroll 10,000 bronchiectasis patients and follow them longitudinally; and the Australian Bronchiectasis Registry (<http://lungfoundation.com.au/health-professionals/bronchiectasis-registry/>). Additionally, efforts to establish bronchiectasis registries are also underway in China, and South America. Patient advocacy organizations such as our stakeholder partners the COPD Foundation and NTMir, as well as foundations focusing on lung disease such as the American Thoracic Society and American Lung Association are currently supporting bronchiectasis education and research in the U.S. All efforts require funding and, many cases, partnerships with pharmaceutical companies. Below are specific steps that the Stakeholder panel agreed will ensure that progress is made on the objectives outlined in this document.

1) Expand data sources and analysis to better understand natural history of bronchiectasis and research priorities.

- Expand the BRR. In response to feedback from the Bronchiectasis Research Consortium and industry partners the BRR will be expanded. The goal is to double the number of patients currently enrolled from 2000 to 4000 within 36 months and to expand the Consortium to include additional sites. In addition to expanding the BRR, the existing BRR data collection forms are being reviewed and modified for a more streamlined and standardized approach to data collection and entry.
- Create a Bronchiectasis and NTM patient-reported registry. Given the need to collect patient-reported outcomes data and that only a sub-set of the individuals with bronchiectasis and/or NTM have the opportunity to join the BRR, the COPD Foundation plans to leverage the BRR and their COPD Patient-Powered Research Network to develop a Bronchiectasis and NTM patient-reported registry.

²⁷T. R. Aksamit et al., "Adult Bronchiectasis Patients: A First Look at the United States Bronchiectasis Research Registry," *Chest* (2016).

2) Tools and evidence are needed to make informed treatment decisions.

- Increase the number of bronchiectasis clinical trials.
 - Use the BRR and Consortium to plan and initiate clinical trials. One goal of the BRR is to support collaborative research and assist in the planning and recruitment for multi-center clinical trials for the treatment of NTM and bronchiectasis.
 - Increase collaborations between researchers, clinicians, patient advocacy organizations, and pharmaceutical companies to develop and test new drugs and formulations. For example, the COPD Foundation has developed an Industry Advisory Consortium for pharmaceutical companies interested in bronchiectasis to collaborate with Bronchiectasis Research Consortium and use the BRR to assist with clinical trials. The Consortium and Registry has already been used for recruitment into 3 major clinical trials.
- Improve understanding of lung microbiome, or patterns of “good/bad” bacteria in lungs.
- Collect blood, tissue, and other samples alongside a registry to allow biomarker identification and validation.
- Develop evidence-based clinical management guidelines that are applicable in the U.S.

3) Increase awareness of bronchiectasis and develop resources for general practitioners and patients. In our needs assessment survey, 36% of respondents selected need for patient information as the top priority for communication about bronchiectasis. The COPD Foundation and NTMir are already working closely with patients and researchers to fill needed gaps in bronchiectasis education and information, and form a centralized online community of bronchiectasis patients on BronchandNTM360social.

- Increase awareness of bronchiectasis among healthcare providers and patients
 - Clinical experts should continue to develop symposia and present timely updates on bronchiectasis management for pulmonologists attending the American Thoracic Society and Chest annual conferences.
 - Develop an evidence-based bronchiectasis curriculum to deliver to local and state organizations of pulmonologists, infectious disease specialists, and internal medicine practitioners.
 - The COPD Foundation is actively working to increase awareness and education in partnership with individuals from the bronchiectasis and NTM clinical leadership. Examples of awareness efforts including convening a patient-centered webinar (for those registered on COPD360social) about bronchiectasis and NTM. The webinar will cover the basics of bronchiectasis and NTM such as manifestations, causes, symptoms, and treatments/therapies, as well as how these two diseases relate to COPD.

- Increase awareness of new resources available to the bronchiectasis and NTM communities
 - Until 2016, bronchiectasis patients lacked a centralized network and patient support system. In response to this critical need identified by the bronchiectasis and NTM community, the COPD Foundation and NTMir developed BronchandNTM360social, an online global social community. BronchandNTM360social is an extensive social networking website which serves as an online home for these communities and provides a comfortable venue to share thoughts and ideas, ask questions, start discussions, read and comment on blogs, and communicate with peers, thought leaders and community managers. Efforts to reach otherwise isolated bronchiectasis patients and invite them to join the community are ongoing.
 - Alternatives for patient support and information exchange are still needed for patients who do not have access to the internet or prefer in-person, local support groups.
- Create patient education resources for bronchiectasis patients
 - Patient information booklets are extremely valuable resources for patients. NTMir has developed “Insight: A Patient’s Perspective” for patients with NTM, and the COPD Foundation is working on a patient booklet “The 1s, 2s, and 3s of Bronchiectasis” targeted for newly diagnosed patients. The booklet is modeled after the successful “1s, 2s, and 3s of COPD” and will be available in printed form and e-download in English and Spanish.
 - Videos are another mechanism to provide accessible information for bronchiectasis patients. The COPD Foundation is planning to develop an educational video series on bronchiectasis, created in partnership with experts in the field and posted on BronchandNTM360social.
 - A third mechanism to provide information to patients is through a telephone information line. The COPD Foundation has a successful C.O.P.D. Information Line, a toll-free service provided for information and referrals on COPD for patients and caregivers impacted by COPD. A similar hotline dedicated to bronchiectasis and NTM could be developed.

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